

**This Page Is Inserted by IFW Operations
and is not a part of the Official Record**

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- **BLACK BORDERS**
- **TEXT CUT OFF AT TOP, BOTTOM OR SIDES**
- **FADED TEXT**
- **ILLEGIBLE TEXT**
- **SKEWED/SLANTED IMAGES**
- **COLORED PHOTOS**
- **BLACK OR VERY BLACK AND WHITE DARK PHOTOS**
- **GRAY SCALE DOCUMENTS**

IMAGES ARE BEST AVAILABLE COPY.

**As rescanning documents *will not* correct images,
please do not report the images to the
Image Problem Mailbox.**

THIS PAGE BLANK (USPTO)

OPI

DATE 08 / 07 92 APPL. ID 9141391
PCT NUMBER PCT/US91/09215

AU 9141391



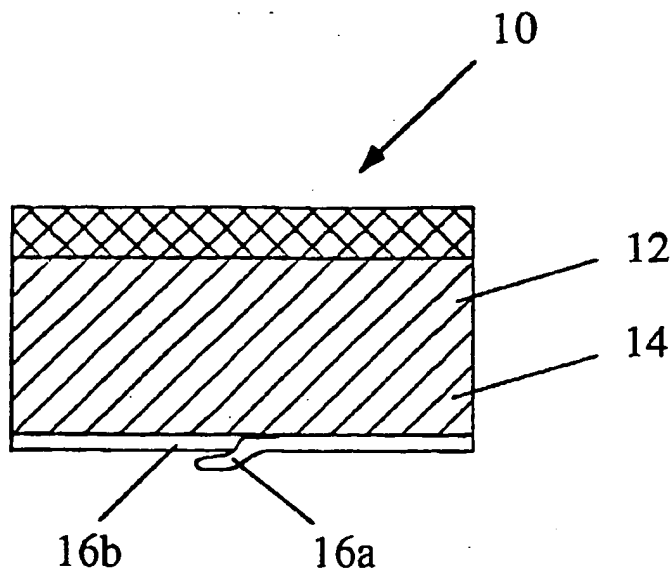
PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁵ : A61F 13/02, 13/00	A1	(11) International Publication Number: WO 92/10154 (43) International Publication Date: 25 June 1992 (25.06.92)
(21) International Application Number: PCT/US91/09215 (22) International Filing Date: 6 December 1991 (06.12.91) (30) Priority data: 625,906 10 December 1990 (10.12.90) US 702,043 17 May 1991 (17.05.91) US (71) Applicant: THERATECH, INC. [US/US]; 417 Wakara Way, Suite 100, Salt Lake City, UT 84108 (US). (72) Inventors: EBERT, Charles, D. ; 558 N. Perry's Hollow Road, Salt Lake City, UT 84103 (US). PATEL, Dinesh ; 5839 S. Meadow Crest Drive, Murray, UT 84107 (US). HEIBER, Sonia ; 1464 Wilton Way, Salt Lake City, UT 84108 (US).	(74) Agent: REED, Dianne, E.; Morrison & Foerster, 545 Middlefield Road, Suite 200, Menlo Park, CA 94025 (US). (81) Designated States: AT (European patent), AU, BE (European patent), CA, CH (European patent), DE (European patent), DK (European patent), ES (European patent), FR (European patent), GB (European patent), GR (European patent), IT (European patent), JP, KR, LU (European patent), MC (European patent), NL (European patent), SE (European patent). Published With international search report.	

(54) Title: METHOD AND SYSTEMS FOR ADMINISTERING DRUGS TRANSDERMALLY USING SORBITAN ESTERS AS SKIN PERMEATION ENHANCERS



(57) Abstract

Skin permeation enhancer compositions are provided which increase the permeability of skin to transdermally administered pharmacologically active agents. The compositions contain a sorbitan ester in addition to the selected pharmacologically active agent and may also contain C₁-C₄ aliphatic alcohol. Methods and drug delivery systems are provided which systems have a laminated matrix or a drug reservoir. In the drug reservoir type of Figure 1, designated (10) there is provided a backing layer (12), a drug reservoir (14) and a two piece release liner (16a) and (16b). In the laminated type, designated (18) in Figure 2, there is provided a backing film (20), a reservoir (22), a ring shaped layer (24) of an adhesive, a membrane layer (26) and a sealable inner liner.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	ES	Spain	MG	Madagascar
AU	Australia	FI	Finland	ML	Mali
BB	Barbados	FR	France	MN	Mongolia
BE	Belgium	GA	Gabon	MR	Mauritania
BF	Burkina Faso	GB	United Kingdom	MW	Malawi
BG	Bulgaria	GN	Guinea	NL	Netherlands
BJ	Benin	GR	Greece	NO	Norway
BR	Brazil	HU	Hungary	PL	Poland
CA	Canada	IT	Italy	RO	Romania
CF	Central African Republic	JP	Japan	SD	Sudan
CG	Congo	KP	Democratic People's Republic of Korea	SE	Sweden
CH	Switzerland	KR	Republic of Korea	SN	Senegal
CI	Côte d'Ivoire	LI	Liechtenstein	SU ⁺	Soviet Union
CM	Cameroon	LK	Sri Lanka	TD	Chad
CS	Czechoslovakia	LU	Luxembourg	TG	Togo
DE*	Germany	MC	Monaco	US	United States of America
DK	Denmark				

+ Any designation of "SU" has effect in the Russian Federation. It is not yet known whether any such designation has effect in other States of the former Soviet Union.

-1-

5 METHOD AND SYSTEMS FOR ADMINISTERING DRUGS TRANSDERMALLY
 USING SORBITAN ESTERS AS SKIN PERMEATION ENHANCERS

Description

10 Technical Field

 The present invention relates generally to the
transdermal administration of pharmacologically active
agents, and more particularly relates to methods and
compositions for enhancing the permeability of the skin
15 to such agents.

Background

 The delivery of drugs through the skin provides
many advantages; primarily, such a means of delivery is a
20 comfortable, convenient and noninvasive way of
administering drugs. The variable rates of absorption
and metabolism encountered in oral treatment are avoided,
and other inherent inconveniences--e.g., gastrointes-
tinal irritation and the like--are eliminated as well.
25 Transdermal drug delivery also makes possible a high
degree of control over blood concentrations of any
particular drug.

 Skin is a structurally complex, relatively
thick membrane. Molecules moving from the environment
30 into and through intact skin must first penetrate the
stratum corneum and any material on its surface. They
must then penetrate the viable epidermis, the papillary
dermis, and the capillary walls into the blood stream or
lymph channels. To be so absorbed, molecules must
35 overcome a different resistance to penetration in each

-2-

type of tissue. Transport across the skin membrane is thus a complex phenomenon. However, it is the cells of the stratum corneum which present the primary barrier to absorption of topical compositions or transdermally administered drugs. The stratum corneum is a thin layer of dense, highly keratinized cells approximately 10-15 microns thick over most of the body.

In order to increase skin permeability, and in particular to increase the permeability of the stratum corneum (i.e., so as to achieve enhanced penetration, through the skin, of the drug to be administered transdermally), the skin may be pretreated with a penetration enhancing agent (or "permeation enhancer", as sometimes referred to herein) prior to application of a drug. Alternatively, and preferably, a drug and a permeation enhancer are delivered concurrently.

The present invention is directed to a novel composition for enhancing the penetration of pharmacologically active agents through skin, the composition based on a sorbitan ester as will be described herein. The composition may or may not contain an aliphatic alcohol as an additional component. The sorbitan ester compositions of the invention have been found by the inventors herein to be particularly effective in enhancing the penetration of pharmaceutically active agents through skin.

While there are a number of patents and publications available which relate to the transdermal administration of drugs and to skin permeation enhancer compositions, applicants are unaware of any art which suggests that sorbitan esters are useful as permeation enhancers in the absence of additional permeation enhancing compounds or which describes the sorbitan ester/aliphatic alcohol compositions as described and claimed herein.

-3-

The systems and methods of the present invention are useful for administering a wide variety of drugs and drug types. For example, one focus of the invention is on the enhanced transdermal administration
5 of steroids.

In another embodiment, the systems and methods of the present invention relate to the transdermal administration of nitroglycerin at enhanced transdermal fluxes. Nitroglycerin is a drug that has been
10 administered as a prompt-acting vasodilator in the relief and treatment of angina pectoris. Nitroglycerin has also been used at somewhat higher doses in the treatment of congestive heart failure. The principal pharmacological
15 action of nitroglycerin is relaxation of vascular smooth muscle, so as to produce a vasodilator effect on both peripheral arteries and veins.

Nitroglycerin was originally administered orally and, later, buccally. More recently, transdermal systems have been developed which have been found to
20 improve the systemic bioavailability of the drug. The Nitro-Dur® Transdermal Infusion System manufactured and sold by Key Pharmaceuticals, Inc. (Kenilworth, New Jersey), the Nitrodisc® made by Searle Pharmaceuticals, Inc. (Chicago, Illinois), the Nitroglycerin Transdermal
25 System of Bolar Pharmaceutical Co., Inc. (Copiague, New York), the Transderm-Nitro® system distributed by CIBA Pharmaceutical Co. (Summit, New Jersey), and the Minitran® system of Riker Pharmaceuticals (St. Paul, Minnesota) are examples of the currently available
30 transdermal nitroglycerin systems.

Several problems which have been encountered with the transdermal administration of nitroglycerin include the tolerance to the drug which results from prolonged administration. Higher and higher doses are
35 required for patients on long-term nitroglycerin therapy,

-4-

necessitating the use of larger and larger transdermal patches. This is obviously inconvenient and undesirable. Accordingly, the present invention is directed to a method and system for administering nitroglycerin transdermally at a relatively high transdermal flux, using a more conveniently sized, smaller patch. The invention may also be useful to treat indications other than angina pectoris, e.g., congestive heart failure or production of controlled hypotension during surgery and perioperative to surgery, which require higher doses of nitroglycerin. The invention involves the transdermal administration of nitroglycerin in combination with a low irritation skin permeation enhancer as will be discussed in detail herein.

Citation of Art

The following references relate to one or more aspects of the present invention.

Skin permeation enhancers, generally: Various compounds for enhancing the permeability of skin are known in the art. U.S. Patent Nos. 4,006,218, 3,551,554 and 3,472,931, for example, respectively describe the use of dimethylsulfoxide (DMSO), dimethyl formamide (DMF) and N,N-dimethylacetamide (DMA) to enhance the absorption of pharmacologically active agents through the stratum corneum. Other compounds which have been used to enhance skin permeability include: decylmethylsulfoxide (C₁₀MSO); diethylene glycol monoethyl ether; polyethylene glycol monolaurate (PEGML; see, e.g., U.S. Patent No. 4,568,343); glycerol monolaurate (U.S. Patent No. 4,746,515); propylene glycol monolaurate; ethanol (e.g., as in U.S. Patent No. 4,379,454); eucalyptol (U.S. Patent No. 4,440,777); lecithin (U.S. Patent No. 4,783,450); the 1-substituted azacycloheptan-2-ones, particularly 1-n-dodecylcyclazacycloheptan-2-one (available under the

-5-

trademark Azone® from Nelson Research & Development Co., Irvine, CA; see U.S. Patent Nos. 3,989,816, 4,316,893, 4,405,616 and 4,557,934); propylene glycol in combination with a fatty acid such as linoleic acid (European Patent Publication No. 261429); "cell envelope disordering compounds" such as methyl laurate or oleic acid in combination with N-(hydroxyethyl) pyrrolidone (U.S. Patent No. 4,537,776); C₃-C₄ diols (U.S. Patent No. 4,552,872, European Patent Application Publication No. 043738); or a binary system of oleic acid, oleins or oleyl alcohol in combination with a lower alcohol (U.S. Patent No. 4,863,970).

Sorbitan analogs as permeation enhancers, specifically: T. Ogiso et al., J. Pharmacobio-Dyn., 9:517-525 (1986), presents studies on percutaneous absorption in vivo and the penetration in vitro of indomethacin. Sorbitan monooleate was tested as a permeation enhancer in combination with a dimethyl sulfoxide (DMSO) gel and was found to have no enhancing effect. T. Ogiso et al., J. Pharm. Sci., 78(4):319-323 (1989), describes the combined use of laurocapram and sorbitan monooleate in a permeation enhancer composition also containing a DMSO gel, for the transdermal administration of indomethacin. W.-W. Shen et al., J. Pharm. Sci., 65(12):1780-1783 (1986), describes the effect of various nonionic surfactants, including sorbitan monopalmitate and sorbitan trioleate, on the percutaneous absorption of salicylic acid. As with the latter two references, the sorbitan esters are used in conjunction with DMSO. U.S. Patent No. 4,637,930 to Konno et al. describes a transdermal formulation for the administration of nicardipine hydrochloride which contains a mixed liquid composed of urea and an additional compound which may be a sorbitan "middle chain" (6-12 carbon atom) fatty acid ester.

-6-

Transdermal administration of nitroglycerin, generally: U.S. Patent No. 4,751,087 to Wick describes an acrylate-based adhesive tape for delivering nitroglycerin transdermally. The system optionally includes as a skin penetration enhancing combination (i) a fatty acid ester, and (ii) glyceryl monolaurate. Patent No. 4,615,699 to Gale et al. describes a transdermal delivery system for administering nitroglycerin in conjunction with ethanol as a skin permeation enhancer. U.S. Patent No. 4,764,381 to Bodor et al. describes nitroglycerin compositions for transdermal administration, containing oleic acid as a permeation enhancer. U.S. Patent No. 4,559,222 to Ensore describes a matrix composition for transdermal drug administration, the matrix containing mineral oil, polyisobutylene, and colloidal silicon dioxide. U.S. Patent No. 4,698,062 to Gale et al. relates to a transdermal drug delivery device which effects "pulsatile" delivery of nitroglycerin to a patient. U.S. Patent No. 4,814,168 to Sablotsky et al. describes transdermal drug delivery systems stated to be useful in the administration of nitroglycerin, the systems containing a "multipolymer" drug reservoir of vinyl acetate, polyethylene, rubber, and a tackifying agent. PCT Publication No. WO83/00093, inventors Keith et al., relates to a polymeric diffusion matrix for the transdermal administration of nitroglycerin which contains two polyvinyl alcohol components and glycerol. PCT Publication No. WO86/00814, inventors Sablotsky et al., relates to an adhesive bilayer transdermal delivery system for the administration of nitroglycerin.

Summary of the Invention

Accordingly, it is a primary object of the invention to provide a method for enhancing the rate of

-7-

penetration of a pharmacologically active agent through the skin.

It is another object of the invention to provide such a method which involves applying to a
5 selected area of intact skin a therapeutically effective amount of the selected pharmacologically active agent in combination with a permeation enhancer composition containing a sorbitan ester.

It is still another object of the invention to
10 provide such a method wherein the permeation enhancer composition consists essentially of: (1) a sorbitan ester; or (2) a sorbitan ester in combination with an aliphatic alcohol as will be described in detail herein.

It is a further object of the invention to
15 provide a skin permeation enhancer composition comprising the pharmacologically active agent and a permeation enhancer composition which consists essentially of: (1) a sorbitan ester; or (2) a sorbitan ester in combination with an aliphatic alcohol.

It is still a further object of the invention
20 to provide a transdermal system in the form of a laminated composite designed to adhere to the skin. The composite contains, in addition to the selected pharmacologically active agent to be administered, a
25 permeation enhancer composition containing a sorbitan ester, and, optionally, an aliphatic alcohol.

It is another object of the invention to provide such a method for administering nitroglycerin transdermally which involves administration of the drug
30 in combination with a low irritation skin permeation enhancer.

It is still another object of the invention to provide a method for administering nitroglycerin transdermally involving administration of the drug with a

-8-

skin permeation enhancer composition as will be defined herein.

It is a further object of the invention to provide such a method in which the nitroglycerin and the skin permeation enhancer are administered simultaneously using a laminated composite as a transdermal patch which contains drug and the selected permeation enhancer in one or more drug reservoir layers.

It is still a further object of the invention to provide a transdermal system for the administration of nitroglycerin which provides for a drug flux of at least about 50% higher than that obtained in the absence of a skin permeation enhancer.

It is yet another object of the invention to provide methods and compositions for the enhanced transdermal administration of steroid drugs.

Additional objects, advantages and novel features of the invention will be set forth in part in the description which follows, and in part will become apparent to those skilled in the art upon examination of the following, or may be learned by practice of the invention.

In one aspect, the invention is a method for administering a pharmacologically active agent transdermally so as to achieve relatively high transdermal fluxes, by administering, through a predetermined area of intact skin and for a predetermined period of time, (1) the agent, and (2) a permeation enhancer consisting essentially of a sorbitan ester, or a sorbitan ester in combination with a C_1 - C_4 aliphatic alcohol. In a preferred embodiment, the skin permeation enhancer and the drug are administered in a single composition. As the clearance rate of many drugs from the body is quite high, it is generally preferred that

-9-

administration be substantially continuous throughout the time period chosen for patch application.

In another aspect of the invention, a composition of matter is provided that is useful for the delivery of a pharmacologically active agent through the skin, comprising:

(a) a therapeutically effective amount of the pharmacologically active agent to be administered; and

(b) an amount of a permeation enhancer composition effective to enhance the penetration of the pharmacologically active agent through the skin, wherein the enhancer consists essentially of a sorbitan ester or a sorbitan ester combined with a C₁-C₄ aliphatic alcohol.

In still another aspect of the invention, a therapeutic system is provided for administering a drug transdermally, at relatively high fluxes as noted above, in the form of a skin patch. The skin patch is preferably in the form of a matrix-type laminated composite containing an upper backing layer that is substantially impermeable to the drug, and at least one drug/enhancer reservoir, one of which forms the basal surface of the device and is designed to adhere to the skin during use. The reservoir is a matrix which contains both the drug and a permeation enhancer as described above. Such a laminated composite preferably includes a strippable protective release liner laminated to the basal surface of the drug reservoir. The release liner is a disposable element designed to protect the exposed reservoir surface prior to use. In an alternative embodiment, a transdermal therapeutic system is provided in the form of a liquid reservoir-type laminated composite, e.g., as described in commonly assigned U.S. Patent No. 4,849,224 to Chang et al., the disclosure of which is incorporated by reference herein.

-10-

In yet another aspect, the invention is a method for administering nitroglycerin transdermally so as to achieve relatively high transdermal fluxes, by co-administering, through a predetermined area of intact skin and for a predetermined period of time, (1) nitro-
5 glycerin, and (2) a permeation enhancer as described herein. In a preferred embodiment, the skin permeation enhancer and the drug are administered in a single composition which contains both components. As the
10 clearance rate of nitroglycerin from the body is quite high, it is preferred that administration be continuous throughout the time period chosen for patch application.

It should also be noted that the present invention is directed to the administration of
15 nitroglycerin to individuals in need of nitroglycerin therapy, generally, and thus encompasses transdermal methods and systems designed for a variety of indications, e.g., the relief and treatment of angina pectoris, congestive heart failure, and the like.

20 In still another aspect of the invention, a therapeutic system is provided for administering nitroglycerin transdermally, at relatively high fluxes as noted above, in the form of a skin patch. The skin patch is a laminated composite containing an upper backing
25 layer that is substantially impermeable to the drug, and at least one drug/enhancer reservoir, one of which forms the basal surface of the device and is designed to adhere to the skin during use. The reservoir contains both the nitroglycerin and a permeation enhancer as described
30 herein.

In still another aspect of the invention, such a laminated composite is provided which further includes a strippable protective release liner laminated to the basal surface of the drug reservoir. The release liner
35 is a disposable element designed to protect the exposed

-11-

reservoir surface prior to use. The release liner, for ease of removal, is preferably a two-part structure in which a first strippable protective sheet partially overlaps a second strippable protective sheet, giving
5 rise to a tab extending from the basal surface of the patch.

Brief Description of the Drawing

Figure 1 is a schematic sectional view through
10 a laminated matrix-type transdermal system of the invention.

Figure 2 is a schematic sectional view through a laminated liquid reservoir-type transdermal system of the invention.

15

Detailed Description of the Invention

Before describing the present compositions, systems and methods of the invention in detail, it is to be understood that this invention is not limited to the
20 particular drugs, sorbitan esters, aliphatic alcohols, or laminate materials described herein as such may, of course, vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to be
25 limiting.

It must be noted that, as used in this specification and the appended claims, the singular forms "a," "an" and "the" include plural referents unless the content clearly dictates otherwise. Thus, for example,
30 reference to a laminated structure containing "a drug" includes a mixture of two or more drugs, reference to "an adhesive" includes reference to one or more of such adhesives, and reference to "a sorbitan ester" includes reference to a mixture of two or more sorbitan esters.

35

-12-

In describing and claiming the present invention, the following terminology will be used in accordance with the definitions set out below.

"Penetration enhancement" or "permeation enhancement" as used herein relates to an increase in the permeability of skin to a pharmacologically active agent, i.e., so as to increase the rate at which the agent permeates into and through the skin. A "permeation enhancer" is a material which achieves such permeation enhancement, and a "penetration enhancing amount" of an enhancer as used herein means an amount effective to enhance skin penetration of a selected agent to a desired degree.

By "transdermal" drug delivery, applicant is using the term in its conventional sense, i.e., to indicate delivery of a drug by passage through the skin and into the blood stream. By "transmucosal" drug delivery, applicant intends delivery of a drug by passage of a drug through the mucosal tissue into the blood stream. "Topical" drug delivery is used to mean local administration of a topical drug as in, for example, the treatment of various skin disorders. These terms will sometimes be used interchangeably herein, i.e., aspects of the invention which are described in the context of "transdermal" drug delivery, unless otherwise specified, can apply to transmucosal or topical delivery as well. That is, the compositions, systems, and methods of the invention, unless explicitly stated otherwise, should be presumed to be equally applicable with any one of these three modes of drug delivery.

The term "drug" or "pharmacologically active agent" as used herein is intended to mean a compound or composition of matter which, when administered to an organism (human or animal) induces a desired pharmacologic and/or physiologic effect by local and/or

-13-

systemic action. In general, the terms include the therapeutic or prophylactic agents in all major therapeutic/prophylactic areas of medicine. Examples of drugs useful in conjunction with the present invention include: anti-infectives such as antibiotics and antiviral agents; analgesics and analgesic combinations; anorexics; antihelminthics; antiarthritics; antiasthmatic agents; anticholinergic agents; anticonvulsants; antidepressants; antidiabetic agents; antidiarrheals; 10 antihistamines; anti-inflammatory agents, antimigraine preparations; anti-motion sickness drugs; antinauseants; antineoplastics; antiparkinsonism drugs; antipruritics; antipsychotics; antipyretics; antispasmodics; anticholinergics; sympathomimetics; xanthine derivatives; 15 cardiovascular preparations including calcium channel blockers and beta-blockers such as pindolol and antiarrhythmics; antihypertensives; diuretics; vasodilators including general coronary, peripheral and cerebral; central nervous system stimulants; cough and cold preparations, including decongestants; steroids; 20 hypnotics; immunosuppressives; muscle relaxants; parasympatholytics; psychostimulants; sedatives; and tranquilizers. For purposes of the aforementioned definition, "drugs" as used herein also include locally administered topical medicaments such as antibacterial agents, antifungals, antimicrobials, cutaneous growth enhancers, antipsoriatics, anti-acne medicaments, and the like.

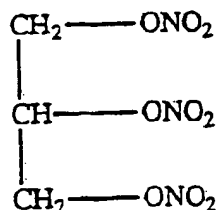
"Carriers" or "vehicles" as used herein refer to carrier materials without pharmacological activity which are suitable for administration in conjunction with the presently disclosed and claimed compositions, and include any such carrier or vehicle materials known in the art, e.g., any liquid, gel, solvent, liquid diluent, 35 solubilizer, or the like. The carriers and vehicles

-14-

suitable herein are "pharmaceutically acceptable" in that they are nontoxic, do not interfere with drug delivery, and are not for any other reasons biologically or otherwise undesirable. Examples of specific suitable carriers and vehicles for use herein include water, mineral oil, silicone, inorganic gels; aqueous emulsions, liquid sugars, waxes, petroleum jelly, and a variety of other oils and polymeric materials.

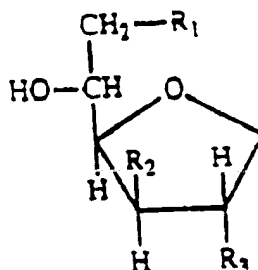
By a "therapeutically effective" amount of a drug or pharmacologically active agent is meant a nontoxic but sufficient amount of the drug or agent to provide the desired therapeutic effect.

"Nitroglycerin" shall mean 1,2,3-propanetriol trinitrate, i.e., the compound having the structural formula



The invention is thus in one embodiment a method for enhancing the rate of penetration of a pharmacologically active agent through the skin, wherein the method involves co-administration of the agent through a predetermined area of intact skin, and for a predetermined period of time, the selected agent and a permeation enhancer consisting essentially of a sorbitan ester or a sorbitan ester in combination with a C₁-C₄ aliphatic alcohol. The sorbitan esters which are useful in conjunction with the present invention have the structure

-15-



5

10 wherein the substituent R_1 has the structure $-O(CO)R'$, where R' is selected from the group consisting of saturated, mono-unsaturated, di-unsaturated and tri-unsaturated aliphatic hydrocarbon substituents of 7 to 21 carbon atoms, preferably 11 to 21 carbon atoms, and may be substituted with 1 to 3 hydroxyl groups. The substituents R_2 and R_3 may be the same or different and are selected from the group consisting of hydroxyl and $-O(CO)R'$ as defined above. R_1 , R_2 and R_3 , may be, for example, lauryl, myristyl, palmityl, stearyl, palmitoleyl, oleyl, linoleyl, linolenyl, or ricinoleyl esters, or the like. Exemplary sorbitan esters are long-chain sorbitan monoesters, wherein R_1 is as defined above, R' is hydrocarbon of 11 to 21 carbon atoms, and R_2 and R_3 are both hydroxyl. Particularly preferred compounds within the class of sorbitan monoesters are sorbitan monooleate and sorbitan monolaurate.

In addition to a sorbitan ester, the permeation enhancer composition of the invention may also include an aliphatic alcohol component. Preferred aliphatic alcohols are the C_1 - C_4 alcohols such as ethanol, *n*-propanol, isopropanol, *t*-butanol, and mixtures thereof. However, longer chain alcohols (typically C_8 - C_{22}) such as oleyl alcohol may also be used (see, e.g., Examples 8 and 9) herein.

-16-

The method of delivery of the present compositions may vary, but necessarily involves application of drug and enhancer to a selected intact surface of the skin or other tissue for a period of time
5 sufficient to provide the desired blood level of drug. The method preferably involves administration of drug and enhancer simultaneously, in a single composition, i.e., as an ointment, gel, cream, or the like, or may involve use of a drug delivery device as taught, for example, in
10 U.S. Patent Nos. 4,849,224, 4,983,395, 4,568,343, 3,797,494 or 3,742,951.

When the drug to be administered and the permeation enhancer as described above are applied in the form of an ointment, gel, cream or the like, the amount
15 of drug contained within the composition will depend on a variety of factors, including the desired rate of delivery, the desired dosage, the disease to be treated, the nature and activity of the drug, the desired effect, possible adverse reactions, the ability and speed of the
20 drug selected to reach its intended target, and other factors within the particular knowledge of the patient and the physician. The amount of enhancer will typically be in the range of 0.1 wt.% to 40 wt.% relative to the total composition, more preferably on the order of about
25 2.5 wt.% to 15 wt.%. The composition may, in addition to drug and enhancer, include one or more selected carriers or excipients, and/or various agents and ingredients commonly employed in dermatological ointments and lotions. For example, fragrances, opacifiers,
30 preservatives, antioxidants, gelling agents, perfumes, thickening agents, stabilizers, surfactants, emollients, coloring agents, and the like may be present so long as they are pharmaceutically acceptable and compatible with the drug and enhancer.

-17-

A transdermal delivery system for the administration of a drug can be constructed with the drug/enhancer composition described hereinabove. Preferred transdermal drug delivery systems for use

5 herein are laminated composites which contain one or more drug/permeation enhancer reservoirs, a backing layer and, optionally, one or more additional layers (e.g., additional drug and/or enhancer reservoirs) as those skilled in the art of transdermal drug delivery will

10 readily appreciate. Figure 1 depicts an exemplary system, generally designated 10, that when applied to skin administers a selected pharmacologically active agent as outlined above. System 10 is a laminated composite in which the top layer 12 is a backing layer,

15 its face forming the top surface of the composite. The drug reservoir, containing drug, enhancer as described herein, and optional carriers or vehicles, is shown at 14, immediately below and adjacent to the backing layer. Prior to use, the laminate also includes a strippable

20 protective release liner. In a preferred embodiment, as described in co-pending commonly assigned Serial No. 07/625,906, filed 10 December 1990, and entitled "Method and Systems for Administering Nitroglycerin Transdermally at Enhanced Transdermal Fluxes," the

25 release liner is in the form of two sheets 16a and 16b, the first sheet 16a partially overlapping the second sheet 16b. Additional structural layers and/or additional drug/enhancer reservoirs may also be present.

The drug reservoir is preferably comprised of a

30 contact adhesive which is a pressure-sensitive adhesive suitable for long-term skin contact. It must also be physically and chemically compatible with the drug and enhancer employed, and with any carriers or vehicles incorporated into the drug/enhancer composition.

35 Further, the adhesive selected for use as the reservoir

-18-

layer must be such that the drug and enhancer are at least somewhat soluble in the adhesive. The drug reservoir will generally be in the range of about 2 to 4 mils in thickness. Suitable adhesives for use as the drug reservoir include polysiloxanes, polyacrylates, polyurethanes, tacky rubbers such as polyisobutylene, and the like. Particularly preferred contact adhesives for use as the drug reservoir herein are cross-linked acrylates (e.g., the Durotak® adhesives, available from National Starch & Chemical Co., New York, NY, or the Gelva® adhesives, available from Monsanto Co., St. Louis, MO).

The backing layer, which is, as shown, adhered to the drug reservoir and serves as the upper layer of the device during use, functions as the primary structural element of the device. The backing layer is made of a sheet or film of a preferably flexible elastomeric material that is substantially impermeable to the drug/enhancer composition. The layer will typically be on the order of 1.0 to about 4.0 mils in thickness, and is preferably of a material that permits the device to follow the contours of the skin, such that it may be worn comfortably on any skin area, e.g., at joints or other points of flexure. In this way, in response to normal mechanical strain, there is little or no likelihood of the device disengaging from the skin due to differences in the flexibility or resiliency of the skin and the device. Examples of polymers useful for the backing layer herein are polyethylene, polypropylene, polyesters, polyurethanes, polyethylene vinyl acetate, polyvinylidene chloride, block copolymers such as PEBAX, and the like. The backing layer may also comprise laminates of one or more of the foregoing polymers.

The release liner is a disposable element which serves only to protect the device prior to application.

-19-

Typically, the release liner is formed from a material impermeable to the drug, vehicle, and adhesive, and which is easily stripped from the contact adhesive that serves as the drug reservoir layer. Preferred release liners
5 for use herein are those which are generally suitable for use in conjunction with pressure-sensitive adhesives. Silanized polyester films are presently preferred.

In a preferred embodiment, as noted above, a two-part release liner is used, wherein a first
10 strippable protective sheet (shown as 16a in Figure 1) partially overlaps a second strippable protective sheet 16b, such that the area of overlap gives rise to a tab which extends from the basal surface of the laminate, enabling ready removal of the strippable sheets from the
15 reservoir layer.

The preferred laminated composites of the invention are as shown in Figure 1, having a backing layer, a drug reservoir, and a two-piece release liner; the drug reservoir contains a drug/enhancer composition
20 as described above, with the quantity of the drug therein, and with the remainder of the drug reservoir comprised of adhesive and optional carriers, vehicles or the like. To use these laminated composites, one is applied directly to the skin of a patient, to release the
25 drug/enhancer composition to the skin, allowing the drug to permeate into the circulation. The adhesive layer which serves as the drug reservoir should be in firm contact with the skin.

In general, such devices are fabricated using
30 methods standard in the art, e.g., solvent-evaporation film casting in which all components of the drug/enhancer composition are admixed with the adhesive which will serve as the drug reservoir, and cast onto a substrate which is either the backing layer or release liner.

-20-

Other layers are then laminated to this initial structure.

In an alternative embodiment, laminated composites containing drug in a liquid reservoir, as described in U.S. Patent No. 4,849,224, may be used. As described in that patent, such devices shown generally at 18 in Figure 2 are comprised of an uppermost layer of a heat-sealable backing film 20 having an inverted, cup-shaped recess that serves the reservoir 22 for the drug-enhancer formulation. The underside of the outer edge of the backing film carries a ring-shaped layer 24 of a pressure-sensitive adhesive peripheral to the reservoir. Underlying the reservoir, just inward of the peripheral ring of adhesive, is a membrane layer 26 that is permeable to the drug-enhancer formulation. A peel sealable inner liner 28 underlies membrane 26 and portions of backing film 20. A peel-sealable release liner 30 covers the entire underside of the assembly and forms the basal surface of the device. Device 18 has a heat seal 32 between the membrane and backing film and a peelable (impermanent) heat seal 34 between the backing film and the inner liner 28. An alternative liquid reservoir-type device which may be used in conjunction with the present compositions is described in U.S. Patent No. 4,983,395, also incorporated by reference herein.

Preferred daily dosages obtained with the present methods and systems will, similarly, vary with the drug administered. The targeted daily dosage will depend on the individual being treated, the indication addressed, the length of time the individual has been on the drug, and the like.

Turning now to the administration of nitroglycerin, specifically, it is preferred that the drug and the selected permeation enhancer or enhancers are administered to the individual simultaneously, in a

-21-

single composition. As with other drugs, a preferred mode of administration, however, is via a transdermal patch, wherein the preferred quantities of the various components will be outlined below.

5 In a preferred embodiment, the nitroglycerin and the selected permeation enhancer or enhancers are administered such that flux is increased by at least about 50% relative to that which would be achieved in the absence of a permeation enhancer, that is, typically, a
10 flux on the order of at least about $10 \mu\text{g}/\text{cm}^2/\text{hr}$, preferably at least about $20 \mu\text{g}/\text{cm}^2/\text{hr}$, most preferably at least about $30 \mu\text{g}/\text{cm}^2/\text{hr}$, is achieved. It will be appreciated by those skilled in the art of transdermal drug delivery that the foregoing numbers are approximate,
15 as transdermal flux may vary with the individual undergoing treatment as well as the particular skin site chosen for transdermal drug delivery.

It is also preferred that the time period for nitroglycerin administration be on the order of 12 to 36
20 hours, optimally about 12 to 24 hours, during which time drug delivery is substantially continuous.

Preferred daily dosages obtained with the present methods and systems are typically in the range of 2.5 to 50 mg, more typically in the range of about 2.5 to
25 20 mg, for nitroglycerin. The targeted daily dosage will, however, depend on the particular drug being administered, the individual being treated, the indication addressed, the length of time the individual has been on the drug, and the like. Generally, and as
30 noted above, the present methods and systems enable transdermal administration of nitroglycerin at somewhat higher transdermal fluxes than enabled with the majority of previously known transdermal nitroglycerin systems, and may thus be useful for treating disorders which
35 require a higher daily dosage than is typical (e.g.,

-22-

congestive heart failure), or for treating patients who have developed some tolerance for the drug. The invention also enables the use of conveniently sized small patches.

- 5 Transdermal delivery of nitroglycerin with the permeation enhancers of the invention enable the use of a skin area for drug administration in the range of approximately 1.0 cm^2 to about 100 cm^2 . At higher transdermal fluxes, smaller skin areas within the
- 10 aforementioned range may be targeted, i.e., less than about 25 cm^2 or, more preferably, less than about 10 cm^2 .

Experimental

- The following examples are put forth so as to
- 15 provide those with ordinary skill in the art with a complete disclosure and description of how to formulate compositions and systems of the invention, and are not intended to limit the scope of what the inventors regard as their invention. Efforts have been made to ensure
- 20 accuracy with respect to numbers used (e.g., amounts, temperatures, etc.), but some experimental errors and deviations should be allowed for. Unless indicated otherwise, parts are parts by weight, temperatures are in degrees Centigrade, and pressure is at or near
- 25 atmospheric.

- Estradiol, norethindrone acetate, progesterone and pindolol were obtained from Sigma Chemical Co., St. Louis, MO. Polyacrylate adhesive solutions were obtained from National Starch & Chemical Co., New Jersey (Durotak®
- 30 80-1194, 80-1054, 80-1070) and from Monsanto Corporation, St. Louis, MO (Gelva® 737). Sorbitan monooleate, sorbitan monolaurate and sorbitan trioleate were all obtained from ICI Americas. Ethanol (USP 95%) was obtained from Fisher Scientific.

-23-

Adhesive laminates were formulated by mixing the selected polyacrylate solutions with drug and/or enhancer, followed by evaporation of solvent. The concentrated solution was cast onto the silanized surface of a polyester release liner (Release Technologies, 2-EST-A-S242M), using a 10 mil gap Gardner knife. The cast adhesive was then dried at 80°C for 15 minutes in a convection oven to yield a final 0.050 inch thick adhesive coating. A 0.0075 inch thick low density polyethylene film (Schoeller Technical Paper Co., New York) was then laminated onto the dried adhesive surface to produce a three-layer transdermal matrix system construction.

The in vitro skin flux of the particular drugs tested was evaluated across human cadaver skin as described by Merrit and Cooper (J. Controlled Release (1984) 1:161) using a high-performance liquid chromatography (HPLC) assay. For these studies the release liner was removed from a previously cut section of the above transdermal matrix construction. The adhesive matrix was then positioned onto the stratum corneum surface of heat separated human epidermis and the skin, with the adhering transdermal system, was then immediately mounted onto the diffusion cell. The steady state flux ($\mu\text{g}/\text{cm}^2/\text{hr}$) of drug was determined by linear regression analysis of the cumulative amount of drug permeating ($\mu\text{g}/\text{cm}^2$) across the skin as a function of the time (hr).

30

35

-24-

Example 1

The aforementioned procedure was used to evaluate the effect of increasing sorbitan ester levels on estradiol flux from acrylic adhesives. The sorbitan ester used was sorbitan monolaurate ("SML"); the acrylic adhesive used was Durotak® 80-1194 ("1194").

Results are set forth in Table I. As may be seen, the flux obtained was found to increase with increasing quantities of sorbitan monolaurate.

Table I

Effect of Increasing Sorbitan Monolaurate
Levels on Estradiol Flux from an Acrylic Adhesive

<u>Enhancer System</u>	<u>Estradiol Conc.</u> <u>(mq/ml)</u>	<u>Flux</u> <u>($\mu\text{g}/\text{cm}^2/\text{hr}$)</u>
None	2 wt.%	0.26 ± 0.05
5 wt.% SML	2 wt.%	0.34 ± 0.09
10 wt.% SML	2 wt.%	0.43 ± 0.08

Example 2

The procedure of Example 1 was followed to evaluate the effect of sorbitan monooleate ("SMO") and sorbitan monolaurate on estradiol flux from three different acrylic adhesive matrices, Durotak® 80-1194 ("1194"), Durotak® 80-1054 ("1054") and Durotak® 80-1070 ("1070"). All systems tested contained 4 wt.% estradiol. As may be deduced from the results set forth in the following table, the two sorbitan esters were found to significantly increase flux in all three types of adhesive matrices.

-25-

Table II
Effect of Sorbitan Esters on Estradiol Flux
From Three Different Acrylic Adhesive Matrices

	<u>Formulation</u>	<u>Flux ($\mu\text{g}/\text{cm}^2/\text{hr}$)</u>
5	1194	0.38 ± 0.36
	1194/15% SMO	1.69 ± 0.58
	1194/15% SML	0.96 ± 0.47
10	1054	0.55 ± 0.12
	1054/15% SMO	0.95 ± 0.40
	1054/15% SML	1.07 ± 0.07
15	1070	0.41 ± 0.07
	1070/15% SMO	0.68 ± 0.13
	1070/15% SMO	0.99 ± 0.31

20 Example 3

The procedure above was followed to prepare additional acrylic adhesive matrices containing estradiol (both with and without a sorbitan ester), so as to evaluate the effect of drug loading on estradiol flux.

25 The acrylic adhesive used was Durotak® 80-1070 ("1070"), and the sorbitan ester used was sorbitan monooleate. Results are set forth in Table III. Sorbitan monooleate was found to increase estradiol flux in both of the systems tested.

30

35

-26-

Table III

Effect of Drug Loading on Estradiol
Flux from an Acrylic Adhesive Matrix
With and Without Sorbitan Monooleate

Formulation	Skin 1	Skin 2
	($\mu\text{g}/\text{cm}^2/\text{hr}$)	($\mu\text{g}/\text{cm}^2/\text{hr}$)
1 wt.% estradiol, no enhancer	0.22 ± 0.08	0.34 ± 0.03
2 wt.% estradiol, no enhancer	0.56 ± 0.08	0.72 ± 0.09
1 wt.% estradiol, 5 wt.% SMO	0.43 ± 0.18	0.55 ± 0.07
2 wt.% estradiol, 5 wt.% SMO	1.00 ± 0.16	0.98 ± 0.08

Example 4

The procedure above was followed to prepare additional acrylic adhesive matrices (Durotak® 80-1194) containing estradiol. One system was prepared with sorbitan trioleate ("STO") as an enhancer, and a second system was prepared without sorbitan trioleate. The flux obtained with the sorbitan trioleate system was approximately 52% higher than that obtained with the control system. Results are set forth in Table IV.

Table IV

Effect of Sorbitan Trioleate
on Estradiol Flux ($\mu\text{g}/\text{cm}^2/\text{hr}$) from
an Acrylic Adhesive Matrix

Formulation	Flux ($\mu\text{g}/\text{cm}^2/\text{hr}$)
4 wt.% estradiol, no enhancer	0.78 ± 0.13
4 wt.% estradiol, 10 wt.% STO	1.19 ± 0.13

-27-

Example 5

The procedure above was followed to prepare acrylic adhesive matrices (Durotak® 80-1194 and 80-1054) containing 10 wt.% norethindrone acetate. Systems were prepared with and without 15 wt.% sorbitan ester; both sorbitan monooleate and sorbitan monolaurate were tested, as shown in Table V. As may be concluded from the results summarized in the table, both sorbitan monooleate and sorbitan monolaurate significantly increased norethindrone acetate flux in both adhesive systems.

Table V

Effects of Sorbitan Esters on Norethindrone
Acetate Flux from Acrylic Adhesives Matrices

15

<u>Formulation</u>	<u>Skin 1</u>	<u>Skin 2</u>
	<u>($\mu\text{g}/\text{cm}^2/\text{hr}$)</u>	<u>($\mu\text{g}/\text{cm}^2/\text{hr}$)</u>
1194/no enhancer	0.21 \pm 0.02	0.24 \pm 0.02
1194/15% SMO	0.38 \pm 0.20	0.31 \pm 0.01
20 1194/15% SML	0.43 \pm 0.09	0.60 \pm 0.03
1054/no enhancer	-	0.27 \pm 0.06
1054/15% SMO	-	0.40 \pm 0.11
1054/15% SML	-	0.54 \pm 0.06

25

Example 6

The procedure above was followed to prepare acrylic adhesive matrices using Gelva® 737 ("737") containing 5 wt.% pindolol. Systems were prepared with 15 wt.% sorbitan monooleate, 15 wt.% sorbitan monolaurate, and 15 wt.% sorbitan trioleate, and compared with a system not containing any sorbitan ester. Again, the flux of drug was found to be significantly higher for all of the systems formulated with the sorbitan esters,

35

-28-

relative to the control. Results are set forth in Table VI.

Table VI

Effects of Sorbitan Esters on Pindolol
Flux from Acrylic Adhesive Matrices

	<u>Formulation</u>	<u>Flux ($\mu\text{g}/\text{cm}^2/\text{hr}$)</u>
	737/no enhancer	0.23 ± 0.05
10	737/15% SMO	0.55
	737/15% SML	0.75 ± 0.26
	737/15% STO	0.55 ± 0.19

Example 7

Flux of progesterone from ethanolic solutions of the drug was evaluated as follows.

Ethanol/water/glycerin/sorbitan ester ointments were prepared as summarized in Table VII, and the flux of the drug therefrom evaluated.

Table VII

Progesterone Flux From Ethanolic
Solutions Containing Sorbitan Ester

	<u>EtOH</u>	<u>H₂O</u>	<u>Glycerin</u>	<u>SMO</u>	<u>SML</u>	<u>Flux</u> <u>$\mu\text{g}/\text{cm}^2/\text{hr}$</u>
25	--	88	10	2	--	0.61 ± 0.03
	--	88	10	--	2	1.21 ± 0.19
	60	30	10	--	--	6.29 ± 0.77
30	60	28	10	2	--	13.04 ± 1.52
	60	28	10	--	2	10.33 ± 4.02

The data summarized in Table 7 clearly demonstrates a synergistic enhancement for progesterone

-29-

when ethanol is combined with sorbitan monolaurate or sorbitan monooleate.

Example 8

5 Nitroglycerin in ethanol (10 vol.%) was obtained from ICI Americas, Inc., Delaware; polyacrylate adhesive solution (Durotak® 80-1194) was obtained from National Starch & Chemical Co., New Jersey. Oleyl alcohol was obtained from Henkel Corp., La Grange,
10 Illinois (HD Eutanol, ultra pure grade). The polyacrylate adhesive solution, nitroglycerin solution and oleyl alcohol were mixed in the required proportion to provide a final solution which upon solvent evaporation would contain 37.5 wt.% nitroglycerin, 5 wt.%
15 oleyl alcohol and 57.5 wt.% polyacrylate adhesive. This solution was rotoevaporated to increase its viscosity to facilitate casting as a film. The concentrated solution was cast onto the silanized surface of a polyester release liner (Release Technologies, 2-EST-A-S242M),
20 using a 10 mil gap Gardner knife. The cast adhesive was then dried at 80°C for 15 minutes in a convection oven to yield a final 0.0025 inch thick adhesive coating. A 0.0025 inch thick low density polyethylene film (Schoeller Technical Paper Co., New York) was then
25 laminated onto the dried adhesive surface to produce a three-layer transdermal matrix system construction. Following the same procedure outlined above, another transdermal matrix system with the final composition of 35 wt.% nitroglycerin and 65 wt.% polyacrylate adhesive
30 was prepared. This matrix did not contain any enhancer. As controls, the flux of nitroglycerin from an unenhanced nitroglycerin patch (NitroDur II, Key Pharmaceuticals) and an enhanced nitroglycerin patch (Minitran®, Riker Pharmaceuticals) were evaluated in
35 parallel.

-30-

Table VIII
HPLC Assay Method for Nitroglycerin

5	Mobile Phase:	50% (vol.) acetonitrile 50% (vol.) water
	Flow Rate:	1.3 ml/minute
	Column:	Partisphere C ₁₈ (Whatman)
	Injection Volume:	20 µl
10	Wave Length:	210 nm
	Retention Time:	3.0 minutes
	Run Time:	5.0 minutes

15 Table IX provides the skin flux in two
different experiments obtained from the controls and the
transdermal matrix patches prepared according to the
method described above. The flux obtained from the oleyl
alcohol matrix is much higher than that from the
20 unenhanced NitroDur II control patch and the unenhanced
nitroglycerin patch prepared as described above.
Furthermore, the oleyl alcohol matrix produced
significantly higher nitroglycerin skin flux than the
enhanced control patch, Minitran.

25

30

35

-31-

Table IX
Nitroglycerin Skin Flux
 ($\mu\text{g}/\text{cm}^2/\text{hr}$)^a

	<u>Formulation</u>	<u>Skin 1</u>	<u>Skin 2</u>
5	NitroDur II	20.58 \pm 2.60	29.92 \pm 4.02
	Minitran	26.63 \pm 5.92	36.69 \pm 2.91
	65/35 ^b	24.21 \pm 2.84	30.68 \pm 2.80
	57.5/37.5/5 ^c	38.56 \pm 0.96	45.63 \pm 4.33

10 ^a N = 4, mean \pm standard deviation

^b weight percent of adhesive/nitroglycerin (no enhancer)

^c weight percent of adhesive/nitroglycerin/oleyl alcohol

Example 9

15 Nitroglycerin was premixed into the National
 Starch Durotak® 80-1194 polyacrylate adhesive by Atlas
 Powder Company to provide a final solution containing
 22.1 wt.% nitroglycerin, 35.8 wt.% solid acrylic adhesive
 and, 42.1 wt.% total solvents. Oleyl alcohol (Henkel) or
 20 sorbitan monooleate ("Arlacel® 80"; ICI Americas) was
 then dissolved into the nitroglycerin/adhesive solution
 at various levels to provide final matrix compositions
 ranging from 0 to 7.5 wt.% enhancer upon drying. These
 solutions were then cast onto silanized release liners,
 25 dried at 80°C for 15 minutes, and finally laminated onto
 the polyethylene backing film as described in the
 preceding example. Transdermal nitroglycerin delivery
 was then determined as a function of enhancer loading as
 described in the Example 8 using the Minitran Patch
 30 (Riker Labs) as a control. Results are presented in
 Table III.

-32-

Table III
Nitroglycerin Skin Flux
 $(\mu\text{g}/\text{cm}^2/\text{hr})^a$

	<u>Formulation</u>	<u>Oleyl Alcohol</u>	<u>Arlacel 80</u>
5	60.0/37.5/2.5 ^b	39.61 \pm 1.94	39.18 \pm 4.28
	58.75/36.25/5.0 ^b	41.27 \pm 4.65	42.63 \pm 7.55
	57.25/35.25/7.5 ^b	47.02 \pm 2.63	36.04 \pm 8.13
	Minitran Control	31.52 \pm 1.79	31.52 \pm 1.79
10	^a N=4		
	^b weight percent ratios of adhesive/nitroglycerin/enhancer		

In general, nitroglycerin flux was found to increase with increasing enhancer (either oleyl alcohol or Arlacel 80) content. Further, higher nitroglycerin flux values were observed with all enhancer loadings in the experimental matrix compositions than with the Minitran control.

20

Example 10

The procedure of Example 9 is repeated using sorbitan monolaurate in place of sorbitan monooleate (e.g., "Arlacel® 20" from ICI Americas). Enhanced transdermal flux relative to an unenhanced nitroglycerin system is obtained.

25

Example 11

The procedure of Example 9 is repeated using sorbitan monopalmitate in place of sorbitan monooleate (e.g., "Arlacel® 40" from ICI Americas). Enhanced transdermal flux relative to that obtained from with an unenhanced nitroglycerin system is obtained.

30

35

-33-

Example 12

The procedure of Example 9 is repeated using sorbitan trioleate in place of sorbitan monooleate (e.g., "Arlacel® 85" from ICI Americas). As with the preceding examples, the transdermal flux obtained is higher than that which would be obtained for an unenhanced nitroglycerin patch.

Example 13

The enhanced transdermal delivery of nitroglycerin from acrylic matrices containing 5 wt.% enhancer (oleyl alcohol or Arlacel® 80) was evaluated using 3 different donor skins. Enhanced nitroglycerin matrices were prepared as described in Example 9, nitroglycerin skin flux was determined as described in Example 8 using the NitroDur II and Minitran as controls. In vitro skin flux results are presented in Table X.

Table X

Nitroglycerin Skin Flux
($\mu\text{g}/\text{cm}^2/\text{hr}$)

<u>Formulation</u>	<u>Skin 1</u>	<u>Skin 2</u>	<u>Skin 3</u>
NitroDur II	--	26.06 \pm 5.65	16.34 \pm 4.64
Minitran	39.97 \pm 3.69	44.14 \pm 5.95	20.17 \pm 1.61
5% Oleyl Alcohol ^a	55.99 \pm 4.80	50.57 \pm 6.53	30.63 \pm 5.04
5% Arlacel 80 ^a	57.45 \pm 3.81	51.86 \pm 10.72	26.57 \pm 2.78

30

^a 58.7% wt acrylic adhesive, 36.3% wt nitroglycerin, 5.0% wt enhancer

The flux obtained from both oleyl alcohol and Arlacel 80 enhanced matrices was nearly double that

-34-

obtained from the unenhanced NitroDur II control patch. Further, both enhanced matrix formulations produced consistently higher nitroglycerin skin flux than the enhanced control patch, Minitran.

5

Example 14

An easy to open release tab can be prepared by overlapping two sections of the release liner by approximately 1/8 inch. The adhesive/drug/enhancer solution can then be cast onto a first release liner, dried and laminated to the backing film as described in the above examples. The first release liner is then removed and the overlapping release liner is then laminated onto the adhesive surface in its place. Final transdermal patches are then die cut with the overlapping release liner section spatially within the final patch. Alternatively, the first release liner can be control depth slit following the lamination of the backing film. A section of the slit liner is then removed and a new section relaminated onto the exposed adhesive area such that the new liner section overlaps the remaining, slit prior liner which was not removed from the original laminate. Final patches are then die cut as previously described.

25

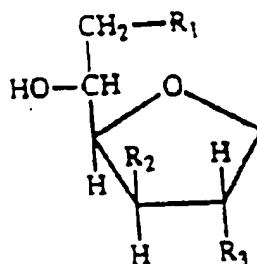
30

35

-35-

Claims

1. A method for enhancing the rate of
5 penetration of a pharmacologically active agent through
the skin, comprising applying to a selected area of
intact skin: (a) a therapeutically effective amount of
the pharmacologically active agent; and (b) a permeation
enhancer consisting essentially of a sorbitan ester.
- 10 2. The method of claim 1 wherein the sorbitan
ester has the structural formula



wherein R_1 has the formula $-O(CO)R'$, R' is selected from
the group consisting of saturated, mono-unsaturated,
di-unsaturated, or tri-unsaturated aliphatic hydrocarbon
25 substituents of 7 to 21 carbon atoms optionally
containing 1 to 3 hydroxyl groups, and R_2 and R_3 are
independently selected from the group consisting of
hydroxyl and $-O(CO)R'$.

- 30 3. The method of claim 2 wherein R' is
selected from the group consisting of saturated, mono-
unsaturated, di-unsaturated, or tri-unsaturated aliphatic
hydrocarbon substituents of 11-21 carbon atoms optionally
containing 1-3 hydroxyl groups, and R_2 and R_3 are both
35 hydroxyl.

-36-

4. The method of claim 3 wherein the sorbitan ester is selected from the group consisting of sorbitan monooleate, sorbitan monolaurate, and mixtures thereof.

5

5. The method of claim 1 wherein the pharmacologically active agent is a steroid.

6. The method of claim 5 wherein the steroid is selected from the group consisting of estradiol, progesterone, norethindrone acetate, and mixtures thereof.

10

7. The method of claim 1 wherein the pharmacologically active agent is pindolol.

15

8. The method of claim 1, wherein the pharmacologically active agent is nitroglycerin.

20

9. A method for enhancing the rate of penetration of a pharmacologically active agent through the skin, comprising applying to a selected area of intact skin: (a) a therapeutically effective amount of the pharmacologically active agent; and (b) a permeation enhancer consisting essentially of a sorbitan ester and a C₁-C₄ aliphatic alcohol.

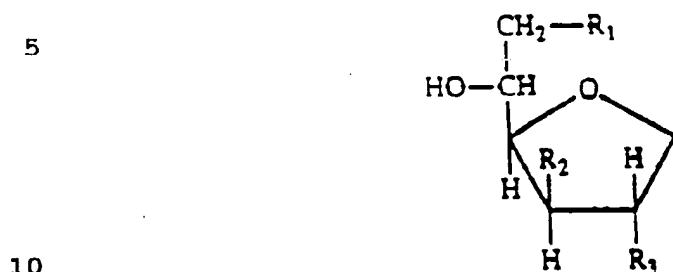
25

30

35

-37-

10. The method of claim 9 wherein the sorbitan ester has the structural formula



wherein R_1 has the formula $-O(CO)R'$, R' is selected from the group consisting of saturated, mono-unsaturated, di-unsaturated, or tri-unsaturated aliphatic hydrocarbon substituents of 7 to 21 carbon atoms optionally
15 containing 1 to 3 hydroxyl groups, and R_2 and R_3 are independently selected from the group consisting of hydroxyl and $-O(CO)R'$.

20 11. The method of claim 10 wherein R' is selected from the group consisting of saturated, mono-unsaturated, di-unsaturated, or tri-unsaturated aliphatic hydrocarbon substituents of 11-21 carbon atoms optionally containing 1-3 hydroxyl groups, and R_2 and R_3 are both
25 hydroxyl.

12. The method of claim 11 wherein the sorbitan ester is selected from the group consisting of sorbitan monooleate, sorbitan monolaurate, and mixtures thereof.
30

13. The method of claim 9 wherein the C_1 - C_4 aliphatic alcohol is selected from the group consisting of ethanol, *n*-propanol, isopropanol, *t*-butanol, and
35 mixtures thereof.

-38-

14. The method of claim 9, wherein the pharmacologically active agent and the enhancer are present in a single pharmaceutical composition, and
5 wherein the composition further includes a pharmaceutically acceptable inert vehicle.

15. A composition of matter for the transdermal administration of a pharmacologically active agent, comprising: (a) a therapeutically effective amount
10 of the pharmacologically active agent; and (b) a permeation enhancer consisting essentially of a sorbitan ester.

16. A composition of matter for the transdermal administration of a pharmacologically active agent, comprising: (a) a therapeutically effective amount
15 of the pharmacologically active agent; and (b) a permeation enhancer consisting essentially of a sorbitan ester and a C₁-C₄ aliphatic alcohol.
20

17. A laminated composite for administering a pharmacologically active agent through a selected area of skin over a sustained time period, comprising:

- 25 ~~(a) a backing layer that is substantially~~ -----
impermeable to the pharmacologically active agent,
(b) a reservoir layer comprising an adhesive polymer, the basal surface of the reservoir layer being adapted to be adhered to the skin, and
30 (c) a therapeutically effective amount of the pharmacologically active agent, and
(d) a permeation enhancer which consists essentially of a sorbitan ester.

-39-

18. A laminated composite for administering a pharmacologically active agent through a selected area of skin over a sustained time period, comprising:

- (a) a backing layer that is substantially
5 impermeable to the pharmacologically active agent,
- (b) a reservoir layer comprising an adhesive polymer, the basal surface of the reservoir layer being adapted to be adhered to the skin, and
- (c) a therapeutically effective amount of the
10 pharmacologically active agent, and
- (d) a permeation enhancer which consists essentially of a sorbitan ester and a C₁-C₄ aliphatic alcohol.

15

20

25

30

35

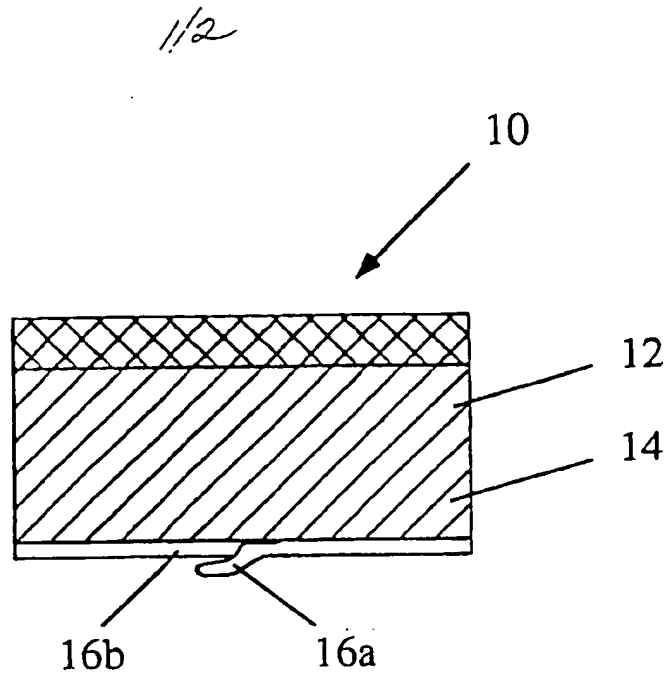


Figure 1

2/2

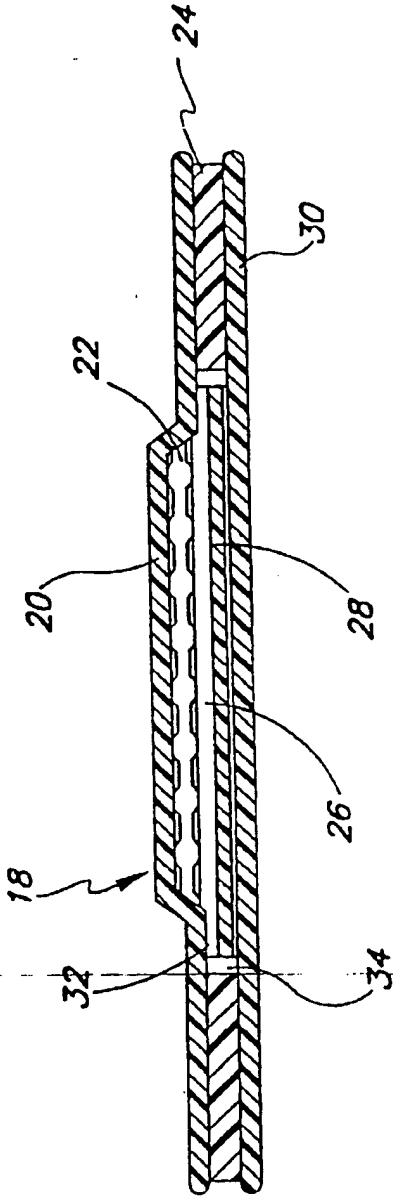


FIG. 2

INTERNATIONAL SEARCH REPORT

International Application No. PCT/US91/09215

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) ⁶		
According to International Patent Classification (IPC) or to both National Classification and IPC		
IPC (5): A61F 13/02, 13/00		
U.S. CL. 424/448		
II. FIELDS SEARCHED		
Minimum Documentation Searched ⁷		
Classification System	Classification Symbols	
U.S.	424/448, 449; 514/946	
Documentation Searched other than Minimum Documentation to the extent that such documents are included in the fields searched ⁸		
III. DOCUMENTS CONSIDERED TO BE RELEVANT ⁹		
Category ¹⁰	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³
Y	US, A, 4,751,087 (WICK) 14 JUNE 1988 See column 5, lines 10 et seq.	1-18
Y	US, A, 4,685,911 (KONNO ET AL) 11 AUGUST 1987 See column 2, lines 44 et seq.	1-18
<p>Special categories of cited documents: ¹⁴</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"&" document member of the same patent family</p>		
IV. CERTIFICATION		
Date of the Actual Completion of the International Search	Date of Filing of this International Search Report	
13 February 1992	14 APR 1992	
International Searching Authority	Signature of Authorized Officer	
ISA/US	Leon R. Horne	